NRA status in the world and impact on viability of vaccine production and global vaccine supply

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WHO HQ Geneva
Acronyms used

- NRA : National Regulatory Authority
- NCL: National Control Laboratory
- EPI: Expanded Programme on Immunization
- DCVRN: Developing Countries Vaccine Regulatory Network
- GLO: Global Training Opportunities (former GTN)
- GTN: Global Training Network
- PQ: Prequalification
- DCVMN: Developing Countries Vaccine Manufacturers
- CT: Clinical trials
- GMP: Good Manufacturing Practices
- GCP: Good Clinical Practices
- PMS: Post Marketing Surveillance
- AEFI: Adverse Events Following Immunization
- CTD: Common Technical Document promoted by ICH

ICH: International Conference on Harmonization
Outline

1. Stratus of NRA: functionality and performance
2. Impact on viability of vaccine production: Domestic and export market
3. Impact on global vaccine supply:
4. Discussions to the DCVMN
Quality of vaccines: terminology

- Highest quality
- High quality
- Known good quality
- Good quality
- Safe
- Efficacious
Quality of vaccines: terminology

Highest quality
High quality  Safe
Known good quality
Good quality
Based on WHO definition published in Vaccine Quality - can a single standard be defined? Vaccine 2956 (2001) 1-4, states that a vaccine of assured quality is a vaccine that is:

1) PRODUCED IN A COUNTRY THAT HAS AN INDEPENDENT AND FUNCTIONAL REGULATORY AUTHORITY MEETING ALL WHO RECOMMENDED 6 REGULATORY FUNCTIONS.

and …

2) HAS NO UNRESOLVED REPORTED PROBLEM WITH THE VACCINE LOCALLY PRODUCED OR IMPORTED VACCINE
WHO concept: the six NRA functions

National Regulatory System: Governance / Strategic planning

1. Marketing Authorization (MA) and Licensing Activities

2. Post-marketing activities including surveillance of Adverse Events Following Immunization (AEFI)

3. NRA Lot Release

4. Laboratory access

5. Regulatory Inspections

6. Authorization/Approval of Clinical Trials

7 components, 6 functions, indicators and sub-indicators

**System**

1. Licensing
2. AEFI
3. Lot release
4. Lab. access
5. Regulatory inspections
6. Clinical evaluation

**5. REGULATORY INSPECTIONS**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>PQ</th>
</tr>
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<tbody>
<tr>
<td>1. GMP requirements</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>2. Mandate to regulate and enforce compliance of GMP</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>3. Code of practices and established schemes for conducting inspection at appropriate intervals</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>4. Appropriate expertise/qualifications for inspectors</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>5. Established procedure to monitor inspection process</td>
<td></td>
</tr>
<tr>
<td>6. Provision for monitoring onward distribution as appropriate</td>
<td></td>
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</tbody>
</table>

PQ = Prequalification  
NRA = National Regulatory Authority  
AEFI = Adverse Events Following Immunization
Country Status: 101(52%) out 193 member states with NRA assessed against WHO published indicators, as of 2010

NRA assessment conducted & planned

- NRA assessment completed
- Not yet conducted

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not be full agreement.
## Priority for Implementing Regulatory Functions

<table>
<thead>
<tr>
<th>Regulatory functions</th>
<th>Source of vaccines</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>UN agency</td>
</tr>
<tr>
<td>Regulatory system</td>
<td>✓</td>
</tr>
<tr>
<td>Marketing Authorization &amp; Licensing activities</td>
<td>✓</td>
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<tr>
<td>Postmarketing: AEFI</td>
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<tr>
<td>Lot release</td>
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<tr>
<td>Laboratory access</td>
<td></td>
</tr>
<tr>
<td>Regulatory inspections</td>
<td>Functions undertaken in producing Countries that are functional</td>
</tr>
<tr>
<td>Authorization &amp; monitoring of CTs</td>
<td>✓</td>
</tr>
</tbody>
</table>

CTs: Clinical trials, UN: United Nations, AEFI: Adverse Events Following Immunization
8 out of 14 DCVMN countries have functional NRA
8 out 23 countries with PQ vaccine

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2008
Vaccines prequalified by WHO: Status 2010 (* DCVMN countries)

15 industrialized country mfrs

✓ Australia
✓ Belgium
✓ Canada
✓ Denmark
✓ France
✓ The Netherlands
✓ Germany
✓ Hungary
✓ Italy
✓ Japan
✓ Rep. of Korea*
✓ Switzerland
✓ Sweden
✓ United Kingdom
✓ USA

8 emerging economy country mfrs

✓ Brazil *
✓ Bulgaria
✓ Cuba *
✓ India *
✓ Indonesia *
✓ Russia
✓ Senegal *
✓ Thailand *

24 manufacturers

36 Sites

108 pre-qualified vaccines used in 124 countries

64% global population
59 (31%) OUT OF 193 MEMBER STATES HAVE A FUNCTIONAL NRA TO REGULATE VACCINES

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STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 & 2008

High priority

<table>
<thead>
<tr>
<th>Priority</th>
<th>Producing 97</th>
<th>Producing 08</th>
<th>Procuring 97</th>
<th>Procuring 08</th>
<th>UN agency 97</th>
<th>UN agency 08</th>
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<tbody>
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<td>33%</td>
<td>17%</td>
<td>23%</td>
<td>6%</td>
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<td>6%</td>
<td>15%</td>
<td>39%</td>
<td>32%</td>
<td>82%</td>
<td>88%</td>
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</table>

Medium priority

<table>
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<tr>
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<th>Procuring 97</th>
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<th>UN agency 97</th>
<th>UN agency 08</th>
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<td>17%</td>
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<td>15%</td>
<td>39%</td>
<td>32%</td>
<td>82%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st January 2009
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 - 2008

COUNTRIES PRODUCING VACCINES

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2009
COUNTRIES PRODUCING VACCINES

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2009
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 - 2008

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st december 2008
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA) STATUS OF NRA, 1997 - 2008

Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2008
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
101 COUNTRIES WHO* NRA ASSESSED AND FOLLOWED UP
1996 - 2008

Source: WHO*/IVB**, as of November 2008

*World Health Organization
**Immunization Vaccines and Biologicals
STATUS OF NRA ACCORDING TO THE MAIN SOURCE OF VACCINES
COUNTRIES AND TOTAL POPULATION STATUS

2008

UN AGENCY
1,238 M, 19% (90 countries)

PROCURING
542 M, 8% (55 countries)

PRODUCING
4,880 M, 73% (48 countries)

NRA functional
1,631 M, 24% (33 countries)

NRA not functional
3,249 M, 49% (15 countries)

Population in millions (M)
Source: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2008
<table>
<thead>
<tr>
<th>Countries</th>
<th>Number Manufacturers</th>
<th>WHO prequalified products</th>
<th>NRA functional</th>
<th>Meet WHO GMP</th>
<th>Ongoing production</th>
<th>Plan to expand capacity</th>
<th>Export</th>
<th>Potential for new PQ products</th>
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<tbody>
<tr>
<td>India</td>
<td>12</td>
<td>several</td>
<td>Yes</td>
<td>90% private, 20% public</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, several</td>
<td>VERY HIGH</td>
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<tr>
<td>Indonesia</td>
<td>1</td>
<td>several</td>
<td>Yes</td>
<td>100% public</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<tr>
<td>Brazil</td>
<td>3</td>
<td>several</td>
<td>Yes</td>
<td>100% public and private</td>
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<td>Senegal</td>
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<td>1</td>
<td>Yes</td>
<td>Production stopped but 100% public</td>
<td>No, but will start again in early 2011</td>
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<td>Yes, YF only</td>
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<tr>
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<td>DCVMN countries</td>
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</tr>
</tbody>
</table>

This group of countries will have better environment opportunities to:

- Expand vaccine production
- Scale up existing production
- Meet demand of export market
- Adapt to more stringent quality standards
- Supply additional PQ products
NRA are developing new business model to regulate biologicals

- Expanding and enhancing their Quality Management System and risk benefit/management approach/concept

- Identifying better their customers and defining new services to customers (Public, manufacturers, delivery programme, etc.)

- Increasing internal expertise and developing network of national experts

- Expanding their role in postmarketing surveillance (provision for PMS IV, GMP inspection using risk management approach, NCL lot release data, trend analysis data)

- Collaborative networks through international network, twinning or during parallel product evaluation (India/Canada, Thailand/Australia/US), DCVRN, AVAREF, etc.
Impact on viability of vaccine production: Domestic and export market constraints

- Implementation of CTD for marketing authorisation/licensing
  - Requirements increased through thorough documentation
  - Assessment of product involving expert committees and increase leadership from internal expertise
  - Onsite evaluation linked to Marketing authorisation process
  - Development skills and expertise in evaluation and supervision of clinical trials

- Enforcement of a more stringent GMP
  - Risk approach concept applied to regulatory inspections
  - Environmental monitoring
  - Validation
  - Quality management system consistent with ISO principles
  - Monitoring and tracking of variations
  - Foreign inspections providing opportunities to raise skills
Impact on viability of vaccine production: Domestic and export market

- Expansion of NRA lot release activities
  - Risk approached testing
  - Procuring countries are now implementing also lot release
  - Use of trend analysis data and active monitoring of manufacturer QC deviations

- PMS and AEFI surveillance
  - Increase capacity for AEFI surveillance: India, China, Viet Nam, Senegal will increase oversight of marketed products
  - Better coordination among regulators, manufacturers and immunization surveillance programme improve causality assessment.
Possible impact and challenges

- **Increasing of registration fees is likely to happen:**
  NRA needs to adjust to increasing workload and be more responsive:
  - registration fees varies between 50 USD to max 1,500 USD in developing countries.
  - May be tier pricing fees can be promoted to reduce barriers for DCVMN.

- **Introduction of CTD is likely to increase manufacturer workload and guide manufacturers to strengthen their regulatory affairs teams:**
  - CTD had been introduced and adapted in Egypt, India, Iran, and Thailand in 2009, will be introduced in Viet Nam, All ASEAN countries, Senegal, by end of 2011.
## Areas of emphasis in SEAR regional vaccine policy (2011-2015)

<table>
<thead>
<tr>
<th>Regional Vaccine Policy (2011-2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Guiding principles and lessons learned</td>
</tr>
<tr>
<td>2. Specific policy objectives</td>
</tr>
<tr>
<td>3. Policy framework</td>
</tr>
<tr>
<td>3.1 Vaccine research and development, technology transfer and public private approaches</td>
</tr>
<tr>
<td>3.2 Vaccine selection, introduction, financing based on burden of disease and national prioritization, and NCIP/NITAG recommendations</td>
</tr>
<tr>
<td>3.3 Vaccine quality and regulation</td>
</tr>
<tr>
<td>3.4 Regional vaccine security</td>
</tr>
<tr>
<td>3.5 Human resources development</td>
</tr>
<tr>
<td>3.6 Knowledge centre; information clearing house; centres of excellence with focus on diseases with global eradication/elimination goals</td>
</tr>
<tr>
<td>3.7 National vaccine policy</td>
</tr>
</tbody>
</table>
Special thanks to major contributors

- BMGF for supporting vaccine producing countries and Global/regional coordination
- USAID for supporting INDIAN NRA
- AUSAID for supporting Asean countries
- JICA and MOFWA for supporting Viet Nam
- DFID for supporting training in several countries
- EDCTP for supporting African countries
- EU for supporting NRA assessments in developing countries
- World Bank for supporting training and assessment
- Islamic development Bank for supporting producing countries
- GAVI for supporting Global and regional coordination as well as GAVI countries
- Govt. of Italy for supporting NRA assessments
information sources

- WHO Web site: :http://www.who.int/vaccines-access/
- Reference document: *Strengthening National Regulatory Authorities*
  - Aide-memoire - strengthening national regulatory authorities
  - GPV Policy Statement - vaccine donations, WHO/VSQ/97.05
  - Informal consultation of experts on national regulation of vaccines, WHO/V&B/99.08
  - Policy Statement of the partners of the Global Alliance for Vaccines and Immunization, WHO/V&B/00.25
  - Regulation of vaccines: building on existing drug regulatory authorities, WHO/V&B/99.10
  - Statement on vaccine quality, WHO/VSQ/GEN/96.02 REV 1
  - Training manual: licensing, lot release, laboratory access WHO/V&B/01.16
  - Training manual on the critical regulatory function for vaccines: evaluation of critical performance through authorized trials ,WHO/V&B/03.12
  - Vaccine Quality - can a single standard be defined? Vaccine 2956 (2001) 1-4